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Chapter 1

General Medical Backgrounds

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http://dx.doi.org/10.5772/60096

1.1. General medical introduction

The characteristics and epidemiology of the gastrointestinal diseases, including the peptic ulcer disease, have significantly changed during the past 40–50 years. Previously, physicians' diagnostic possibilities were limited to the patients' complaints, performance in physical examinations and basic X-ray examinations. Diagnosis was based mainly on the subjective (patients' complaints) and objective (physical observations) data obtained from the patients. However, the diagnostic modalities of the everyday medical practice have changed significantly during the past decades resulting in the usage of modern medical diagnostic instruments.

Peptic ulcers and gastrointestinal mucosal damage were accepted as the result of the unbalanced equilibrium between the aggressive (HCl and pepsin) and defensive (blood supply, mucus, bicarbonate, prostaglandins, biochemistry of target organs, etc.) factors. Consequently, the principal role of overproduction of gastric acid secretion and pepsin secretion or decreased defense against gastrointestinal damage (gastric, duodenal and jejunal ulcers) has been accepted as possible causes for the development of gastrointestinal mucosal damage. However, the details of these mechanisms and their key factors have changed over the past decades. The correction of unbalanced equilibrium between the aggressive and defensive factors in the gastrointestinal mucosa gave the basis of therapeutic possibilities in patients with peptic ulcers before the discovery of "gastric cytoprotection" by André Robert (1979). He indicated that prostaglandins prevent the gastric mucosal damage without the presence of gastric inhibitory actions in rats. Earlier, we observed that the duodenal ulcer in patients healed; however, the gastric secretory responses did not change during a prolonged atropine treatment (Mózsik et al., 1965 a, b). We observed this phenomenon in patients with duodenal ulcer, and we gave a clinical pharmacological explanation for the existence of this phenomenon (for details, see Chapter 2).

Conversely, we had very limited treatment options for patients, such as the application of alkaline mineral water, strict diets (which were not known in detail) and a small number of drugs to be applied in medical practice. Many changes have emerged in medical knowledge,

history of patients, civilization, life styles, working and living conditions, nutrition, drug research and the introduction of various medications. We have gained new insight from the physiology, pathology and etiology of diseases and from drug development, nutrition, immunology, biochemistry and other instrumental studies. The genetic code of living cells led to a significant increase in molecular genetics research in medical sciences. Therefore, the correct diagnosis is increasingly becoming the key point of successful therapy.

1.2. Problem- orientated medicine

Since the plat 40–50 years, there has been a significant increase (advantage) in the diagnostic panel for bedside medical practice (endoscopy, ultrasonography, computer tomography, positive emission tomography, angiography, scintigraphy, special immunologically based scintigraphy, etc.). During the same time period, extremely significant advances were observed in the laboratory, such as immunological, histological, immunohistological and genetic diagnostic examinations in everyday medical practices. During this period (mainly during 1970–1980), the different diseases (and our medical activities) were approached by the citation of "problem-orientated medicine," keeping in mind that primary and correct diagnosis was the main aim of everyday medical practice.

The medical treatments including the medical (pharmacological), dietetic, psychological, surgical and others were offered to patients based on the correct diagnosis.

1.3. Evidence-based medicine

We have to note that the evaluation of applied medical therapy was based on the changes in patients' complaints, physicians' opinion, better general health conditions (appearance of the appetite, increase of body weight, better laboratory results, etc). During the past 50 years, the correct methodologies (clinical pharmacology, clinical dietetics, etc.) for critical and objective evaluation of the performed medical treatments were not available.

During the period 1960–1970, we only had the parasympatholytics (atropine, scopolamine and other quaternary ammonium compounds) and different antacids to be used in the medical treatment of peptic ulcer in patients. Furthermore, the new generation of various drugs (for inhibition of gastric acid secretion) – as histamine receptor-blocking agents (from the first to fourth generation), gastrin antagonists, proton pump inhibitors (PPI) and other compounds (prostaglandins, sucralfate, scavengers, etc.) – appeared in the field of medical treatment of patients with classical peptic ulcer disease. The increased gastrointestinal pharmacology led us to learn – in the clinical practice – the terminology of "evidence-based therapy." This terminology still exists; however, the applicability of this medical practice went over a significant change in the plast dcades. The "evidence-based therapy" suggested the existence of its development of human clinical pharmacology by the increase in the emergence of new families of drug compounds. The established clinical pharmacology (form human phase I to human phase IV) during 1960–1970 is given an objective method to crease the "evidence-based medicine." During the first period of clinical pharmacology, the experts analyzed the absorption, metabolization and excretion of different drugs from the gastrointestinal tract; thereafter, the identification of oral/parenteral dose rates was calculated in the case of same drugs, and following these observations, the efficiencies of therapeutic values of drug treatments were

identified in small groups of patients, which extended many thousand patients in multiclinical, multicentric, multinational, randomized and prospective studies all over the world. The organizations of these large-scale studies, involvement (participation) of special patients, special clinical units and using the services of health experts (sisters, laboratory experts and physicians) represented extremely expensive financial requirements, which were covered by the involvement of other large pharmaceutical firms. The small countries (like Hungary) participated in these studies, however, together with others countries.

1.4. Changes in the etiologies and therapies in patients with peptic ulcer

During the past 50 years, the suggested etiological factors for the development of peptic ulcer diseases changed significantly and the medical terminology of peptic ulcer diseases changed as well ["genuine ulcer," secondary ulcer diseases that are associated with the presence of other chronic diseases (such as chronic pulmonary, liver diseases, stress, burn and stroke in the brain), and recently the increased drug consumption for reasons other than the gastrointestinal tract; however, these drugs cause gastrointestinal mucosal damage (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs)) or overconsumption of alcohol]. In the 1980s, the terminology of "non-ulcer dyspepsia (NUD)" was introduced by Scandinavian researchers, which represented those patients who had typical complaints of peptic ulcer, but there was no possibility to detect any alterations (histology, endoscopy) in this group of patients. The gastric mucosal damage caused by different drugs was also introduced in the everyday medical practice.

The number of patients suffering from peptic ulcer diseases also changes over time, and the number of patients suffering from peptic ulcer diseases differs in different countries over the world. In our country (Hungary), the number of patients with peptic ulcer is about 10% of the total Hungarian population (inhabitants) since the 1960s.

We have to accept the changes in the terminology of "peptic ulcer disease." In the 1960s, only the "primary (or genuine)" and "secondary" peptic ulcer diseases were accepted in our medical practice. The patients with secondary peptic ulcer associated with other diseases (stress, sepsis, stroke, pulmonary and liver diseases, burn and trauma), whereas the presence of these factors in the cases of patients with "primary (or genuine)" peptic ulcer diseases was not detected. The "acid-related diseases" also came into medical practice (as diagnosis of patients).

The diagnosis of peptic ulcer disease is based on different objective factors, such as X-ray examination (only in the early period), endoscopic examination and histology.

The classical definition of peptic ulcer disease can be histologically accepted only by the presence of tissue mucosal damage that reaches the muscular mucosal layer. The correct histological definition is necessary for the diagnosis of patients with peptic ulcer diseases. Consequently, the presence of mucosal erosion cannot be considered as a "peptic ulcer disease" (independently from that, the treatment and prevention of these gastrointestinal mucosal injuries represent essential medical problems). After receiving the Nobel Prize in physiology (medicine) by Warren and Marshall (2005), the *Helicobacter pylori*-positive and -negative characterization appeared in patients with the above-mentioned clinical entities.

We have to note that various drugs (including the nonsteroidal anti-inflammatory drugs and others) can cause gastrointestinal diseases (increased complaints of pyrosis in the epigastric

region of the abdomen, vomiting, bleeding, etc.). The correct number of patients with these complaints is not known; however, the number of patients consuming NSAIDs is extremely high. These problems are very important in the our medical practices (looking for the etiology and later the treatment of disease) of medical practices; however, we have to emphasize very well and clearly that these patients are out from the patients with really peptic ulcer disease (because these mucosal damages are in present form out from the classical histological criterion of peptic ulcer disease in patients). These above-mentioned basic criteria of the histological events produced many offered (and gave) many misunderstanding information (results) to know and critically to evaluate thre of the different etiological factors, mechanisms and efficiencies of different medical treatments in patients with classical peptic ulcer diseases.

We have the details of the development of different gastrointestinal mucosal damages (injuries) and the possibilities to prevent these gastric (gastrointestinal) mucosal damages (injuries) through different experimental models in different animal spices.

1.5. Main lines of our research activities in field of peptic ulcer research in peptic ulcer in patients with peptic ulcer and in different animal models

The focus of our research is in accordance with the peptic ulcer research from the 1960s; in the beginning, we had many unresolved and unknown points to be addressed.

We started our research with the patients' problems, and later to other fields such as clinical pharmacology, general biochemistry, molecular pharmacology and biochemistry, oxygen free radicals and antioxidants, specific immunohistochemistry, clinical nutrition, experimental and clinical gastroenterology and nutrition as well as innovative drug research.

Our principal strategy was to understand the problems of patients. As we were not able to understand these problems, we started with animal observations (hoping that we receive correct answers to our questions). We tried answering different and concrete questions in the medical practice.

The research lines in our practice changed over time in the past decades (we started with patients' problems, followed by experimental observations and then back to patients' problems). This research philosophy has been kept in our life. We tried answering different and concrete questions of medical practice and followed this methodology later.

In the pertinent literature, the peptic ulcer disease appeared because of the unbalanced equilibrium between the aggressive and defensive factors in the gastrointestinal mucosa; however, the details of these factors remain to be unknown.

Recently, the possible mechanisms of gastric acid secretory responses have been widely studied in clinical gastroenterology. The extent of gastric basal acid secretory responses (basal acid output, BAO) and acid secretory responses (maximal acid output, MAO) produced by different doses of histamine (given subcutaneously in superliminal but submaximal or superliminal and supermaximal doses) was measured in different groups (gastric, duodenal and jejunal ulcers) of patients with peptic ulcer disease (PUD) (Semb and Myren, 1968). The real reason to study these gastric secretory responses in patients with PUD is that the increased gastric acid secretion has been suggested as one of the different factors, which is responsible for the increased aggressive factors in the gastrointestinal tract. The possible role of pepsin

secretion in the stomach has been suggested to be another aggressive factor for the development of PUD. The increased role of cholinergic dominance (by the increased activity of vagal nerve) is closely associated with the increased gastric acid secretory responses and pepsin production.

In these years, we have no concrete knowledge of the details of defensive factors. The presence of tissue hypoxia of gastroduodenal mucosa of patients with peptic ulcer has been indicated since many years in the ulcer development. Clinically, the presence of tissue hypoxia could be accepted in patients with massive bleeding, whereas no exact observations of gastric mucosal blood flow were carried out in patients during the development of ulcer. Many observations were carried out in animals under different conditions; however, it is interesting to note that the decreased gastric mucosal blood flow was not associated with the presence of tissue hypoxia in terms of biochemistry (increased level of lactate and decreased level of oxidative phosphorylation in the gastrointestinal mucosa).

After a careful survey of the pertinent literature, the research on the evaluation of the details of decreasing activity of vagal nerve in the everyday medical practice in patients with PUD (by parasympatholytic drugs at the beginning of our studies) was started.

During that time, only atropine and scopolamine (the only tertiary ammonium compounds) were used in the everyday medical practice.

Our primary aims of observations were as follows:

1. To establish the clinical pharmacological basis of anticholinergic agents in patients with PUD;
2. To measure the gastric secretory responses of patients with duodenal ulcer before and after (2–4 weeks treatment with atropine) healing of clinically detectable ulcer and
3. To detect the changes in complaints of patients during the medical treatment (especially at the beginning and at the end) (as in complaints of patients originated from the diseases and in the drug-induced side effects – tachycardia, mouth dryness and problems in visual functions).

These studies were carried out in patients with classical duodenal ulcer and were admitted to Second Department of Medicine, University of Debrecen, Hungary.

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